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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/435,257	11/05/1999	PAUL A CLEMONS	385A-US	4970

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EXAMINER	
PARAS JR, PETER	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/435,257	CLEMONS ET AL.
Examiner	**Art Unit**
Peter Paras, Jr.	1632

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2002 and 09 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *19 and 40-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,20,21,23,26,28,32,34,36 and 38* is/are rejected.

7)☒ Claim(s) *12-18,22,24,25,27,29-31,33,35,37,39 and 51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

Applicant's amendment received on 7/22/02 has been entered. Claims 2-3, 12, 28-29, and 35 have been amended. New claim 51 has been added. Claims 1-51 are pending. Claims 1-18, 20-39, and 51 are currently under consideration. Claims 19 and 40-50 have been withdrawn from consideration.

Election/Restrictions

This application contains claims 19 and 40-50 drawn to an invention nonelected with traverse in Paper No. 7. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

It is maintained that the restriction requirement was proper and has been made **FINAL.** It is noted that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Drawings

New corrected drawings are required in this application because of the objections by the Draftsman indicated in the PTO 948 attached to the Office action mailed on 8/3/00. Applicant is advised to employ the services of a competent patent draftsperson

outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Objections

Claims 12-18, 22, 24-25, 27, 29, 31, 33, 35, 37, 39 and 51 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must refer to claims in the alternative and cannot depend from another multiple dependent claim. The previous objection is maintained for the reasons of record advanced on page 2 of the Office action mailed on 1/16/02. Claim 12 does not refer to claims 5-11 in the alternative and claim 51 depends from another multiple dependent claim (claim 12). Claims 13-18, 22, 24-25, 27, 29, 31, 33, 35, 37, and 39 depend from claim 12. See MPEP § 608.01(n). Accordingly, the claims 12-18, 22, 24-25, 27, 29, 30, 31, 33, 35, 37, 39 and 51 have not been further treated on the merits.

Claims 12 and 35 are objected to because of the following informalities: the claims contain brackets, "[ ]", which appear to be typographical errors. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 28 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 28 is directed to an isolated host cell of human origin comprising a claimed nucleotide sequence. A broad interpretation of the claim encompasses human embryonic stem cells, the scope of which encompasses a transgenic human being. A human being is non-statutory subject matter. As such, the recitation of the limitation "non-human" would be remedial for claims 28-29. See 1077 O.G. 24, April 21, 1987.

Applicants have amended the claim to recite an isolated host cell of human origin.

In response, the Examiner asserts that the claim as amended now encompasses human embryonic stem cells, the scope of which embraces a transgenic human being. As recited above, human beings are non-statutory subject matter.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 28, 30, 32, 34, and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in

such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The previous rejection is maintained for the reasons of record advanced on pages 3-7 of the Office action mailed on 1/16/02.

Applicants have argued that a variety of methods and materials for creating transgenic animals were known in the art as of the effective filing date of the instant application. In light of such Applicants further argue that the transgenic art is a reasonably predictable art. In support of their arguments Applicant's submit that many patents have issued, which have claims directed to transgenic non-human animals. See pages 2-4 of the amendment.

In response, the Examiner maintains that the transgenic art is unpredictable with respect to transgene expression and the phenotype resulting from transgene expression. The Examiner agrees that many patents have been issued, which contain claims directed to transgenic non-human animals. However, the difference between the claims of the issued patents and the instant claims is that the issued claims recite a phenotype, which results from transgene expression, for each transgenic non-human animal. Applicant's arguments appear to be off-point because the issue is not whether technology for creating transgenic non-human animals is known or whether transgenic non-human animals can be made. The issue is the phenotypic unpredictability resulting from transgene expression; the evidence of record has not taught a phenotype resulting from expression of a CAB domain in a transgenic non-human animal. The Examiner maintains that the level and specificity of transgene expression and the resulting

phenotype are directly dependent on the specific transgene construct. Moreover, the individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. This observation is supported by Wall and Houdebine. See pages 4-5 of the previous Office action. It is further maintained that transgene expression is not predictable and varies according to the particular host species and specific promoter/gene combination(s) The claims as written are broad and embrace all species of transgenic non-human animals; the claims also do not recite any particular promoter that is used for directing expression a CAB domain in any animal. The art of record supports the unpredictability of transgene expression across species of animals. See Hammer, Ebert, Mullins, Kappel, Wall, and Strojek and Wagner, on pages 5-6 of the previous Office action who all report phenotypic differences in transgenic animals whose genomes comprise the same transgene. Furthermore, the instant specification has not provided a correlation between expression of a CAB domain and a specific resulting phenotype in any host animal. In light of the above it is maintained that the transgenic art is an unpredictable art with respect to transgene expression and resulting phenotype.

Accordingly, the previous rejection is maintained for the reasons of record.

Claims 26, 30, 34, 36, and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell *in vitro* comprising a nucleotide sequence encoding a CAB domain, does not reasonably provide enablement for is not enabling for a host cell *in vivo* comprising a CAB domain protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The previous rejection is maintained for the reasons of record advanced on pages 7-10 of the Office action mailed on 1/16/02.

The claims are interpreted to read on a somatic cell that has been transformed *in vivo* with one of the claimed nucleotide sequences.

Applicant's arguments filed on 7/22/02 have been considered but are not found persuasive. Applicants have argued that the Examiner's concerns about whether gene therapy "works" are off-point. Applicants assert that they are not required to optimize all embodiments of their inventions to suit FDA standards. Applicants go on to further assert that the prior art, at the time the claimed invention was made, provided ample guidance for delivering genes *in vivo* to enable the skilled artisan to practice the invention as claimed. See page 5 of the amendment.

In response, the Examiner maintains that the evidence of record has not provided guidance that correlates expression of a nucleotide sequence encoding a CAB domain in a cell *in vivo* with any particular effect. It is further maintained that the evidence of record has not provided other uses for expressing a nucleotide sequence that encodes a CAB domain in cell *in vivo* other than to provide a therapeutic effect.

See pages 7-8- of the Office action mailed on 1/16/02. The Examiner asserts that the art of gene therapy is unpredictable with respect to expression of a heterologous nucleotide sequence *in vivo* with a therapeutic effect resulting from said expression. The prior art of record supports the Examiner's assertion regarding the state of the art of gene therapy. See Verma, Anderson, Miller, Deonarain, and Crystal on pages 8-10 of the Office action mailed on 1/16/02.

Accordingly, the rejection is maintained for the reasons of record.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 20, 21, 23, 26, 28, 30, 32, 35, 36, and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The previous rejection is maintained for the reasons of record advanced on page 11 of the Office action mailed on 1/16/02.

Applicant's arguments filed on 7/22/02 have been fully considered but are not found persuasive. Applicants have argued that the claims as amended now recite GenBank accession numbers for calcineurin A or calcineurin B nucleotide sequences and thus, provide sequences for calcineurin A and B. See pages 1 and 5 of the amendment.

In response, the Examiner maintains that the claims are indefinite as written for lack of a uniform numbering system of amino acids known in the art and because the specification has not provided a sequence (either amino acid or nucleotide) of either calcineurin A or calcineurin B that defines that claimed sequences. While the claims as amended now recite GenBank accession numbers in order to provide the claimed cal A and cal B sequences, the nucleotide sequences contained within the GenBank accession numbers have not been included in the instant specification as originally filed and more importantly the accession numbers contain cDNA sequences there does not appear to be any uniform numbering system for the peptide sequences recited in the claims. Any attempt to include the sequences of the GenBank accessions is an improper incorporation by reference and is not permissible. Thus, it is maintained that neither the claims nor the specification have defined the cal A or cal B sequences from which the claimed "portions" are obtained. As such the skilled artisan does not know which calcineurin A or calcineurin B sequences correspond to the claimed portions of cal A or cal B rendering the claims indefinite. Claims 4, 20, 21, 23, 26, 28, 30, 32, 35, 36, and 38 depend from claims 2 and 3. Correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4, 11, 20-21, 26, 28, 34 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Guerini et al (PNAS, 1989, 86: 9183-9187). The previous rejection is maintained for the reasons of record advanced on pages 12-13 of the Office action mailed on 1/16/02.

Applicant's arguments filed on 7/22/02 have been fully considered but are not found persuasive. Applicants have argued that Guerini (PNAS) does not teach the claimed invention, particularly a CAB fusion protein that forms a tripartite complex with an FKBP/CAB ligand and an FKBP domain, and more particularly a fusion protein that comprises any portion of calcineurin B. See the amendment on page 5

In response, the Examiner maintains that Guerini et al anticipates the claimed invention. The Examiner asserts that the term portion is interpreted to mean even a single amino acid. See page 12 of the Office action mailed on 1/16/02. In light of such a definition, a nucleotide sequence encoding amino acid residues 12-394, 12-370, or 340-394 of cal A and a single amino acid residue of cal B anticipates the claimed sequences. The teachings of Guerini have provided such a sequence and thus anticipate the claimed invention. See page 12 of the Office action mailed on 1/16/02. Although the claims now recite a GenBank accession number to provide the calcineurin A sequence, however because such is an improper incorporation by reference as stated in the rejection under 35 U.S.C. 112, 2nd paragraph, the instant rejection is maintained. Furthermore, the claim recitation "forms a tripartite complex with an FKBP/CAB ligand and an FKBP domain" appears to be an intended use limitation, which carries little patentable weight for prior art rejections.

Accordingly, the previous rejection is maintained for the reasons of record.

Claims 1 and 3-4, 11, 20-21, 26, 28, 34 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Guerini et al (DNA, 1989, 8(9): 675-682). The previous rejection is maintained for the reasons of record advanced on page 13 of the Office action mailed on 1/16/02.

Applicant's arguments filed on 7/22/02 have been fully considered but are not found persuasive. Applicants have argued that Guerini (DNA) does not teach the claimed invention, particularly a CAB fusion protein that forms a tripartite complex with an FKBP/CAB ligand and an FKBP domain, and more particularly a fusion protein that comprises any portion of calcineurin B. See the amendment on page 5.

In response, the Examiner maintains that Guerini et al anticipates the claimed invention. The Examiner asserts that the term portion is interpreted to mean even a single amino acid. See page 12 of the Office action mailed on 1/16/02. In light of such a definition, a nucleotide sequence encoding amino acid residues 3-170 of cal B and a single amino acid residue of cal A anticipates the claimed sequences. The teachings of Guerini have provided such a sequence and thus anticipate the claimed invention. See page 13 of the Office action mailed on 1/16/02. Although the claims now recite a GenBank accession number to provide the calcineurin B sequence, however because such is an improper incorporation by reference as stated in the rejection under 35 U.S.C. 112, 2nd paragraph, the instant rejection is maintained. Furthermore, the claim recitation "forms a tripartite complex with an FKBP/CAB ligand and an FKBP domain"

appears to be an intended use limitation, which carries little patentable weight for prior art rejections.

Accordingly, the previous rejection is maintained for the reasons of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5-11, 20, 23, 26, 28, 34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guerini et al (PNAS) or Guerini (DNA) taken with Chaudhuri et al (Biochemical and Biophysical Research Communications, 1995, 215(2): 781-790) and Crabtree (U.S. 6,164,787). The previous rejection is maintained for the reasons of record advanced on pages 14-15 of the Office action mailed on 1/16/02.

Applicant's arguments filed on 7/22/02 have been fully considered but are not found persuasive. Applicants argue that the claimed invention is obvious over the combination of references only by hindsight reasoning. Applicants further argue that none of the cited references suggest a fusion protein combining a portion of cal A and a portion of cal B that forms a tripartite complex with an immunophilin or cyclophilin in the presence of a ligand. See pages 5-6 of the amendment.

In response, the Examiner maintains that the claimed invention is obvious over the combination of references. The Examiner asserts that the term portion is interpreted to mean even a single amino acid. See page 14 of the Office action mailed on 1/16/02. In light of such a definition, the sequences of Guerini (PNAS) and Guerini (DNA) meet the sequence limitation of the claims. See the above rejections under 35 U.S.C. 103. Furthermore, the claim recitation "forms a tripartite complex with an FKBP/CAB ligand and an FKBP domain" appears to be an intended use limitation, which carries little patentable weight for prior art rejections.

Accordingly, the claimed rejection is maintained for the reasons of record.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

Art Unit 1632

MICHAEL WILSON
PRIMARY EXAMINER